

**REMARKS**

Claims 1-4, 9-21, 24, 26, and 47-48 are pending in the instant application.

***Withdrawal of Rejections***

Applicants acknowledge the Examiner's withdrawal of rejections 9-21 and 48 for lack of written description.

***Rejection under 35 U.S.C. § 112, 1<sup>st</sup> paragraph***

Claims 1-4, 9-21, 24, 26, and 47-48 are rejected under 35 U.S.C. § 112, 1<sup>st</sup> paragraph for lack of enablement. In the Advisory Action, the Examiner maintained that the Applicants have not enabled the full scope of the claims for various reasons cited in the Advisory Action which are addressed in greater detail below.

Applicants respectfully disagree with the Examiner's contention that the claims not fully enabled for its scope. To comply fully with the enablement requirements of Section 112, first paragraph, a specification must adequately teach how to make and use the claimed invention without undue experimentation.

Under MPEP § 2164.04, the examiner has the initial burden to establish a reasonable basis to question the enablement provided for the claimed invention in order to make a rejection. *See also, In re Wright*, 999 F.2d 1557, 1562 (Fed. Cir. 1993) (examiner must provide a reasonable explanation as to why the scope of protection provided by a claim is not adequately enabled by the disclosure). As stated by the court, "it is incumbent upon the Patent Office, whenever a rejection on this basis is made, to explain why it doubts the truth or accuracy of any statement in a supporting disclosure and to back up assertions of its own with *acceptable evidence or reasoning* which is inconsistent with the contested statement. Otherwise, there would be no need for the applicant to go to the trouble and expense of supporting his presumptively accurate disclosure." *In re Marzocchi*, 439 F.2d 220, 224 (CCPA 1971) (emphasis added).

In the April 11, 2006 Office Action, the Examiner had cited some case law relating to unpredictability and enablement (middle of page 4) and then made a conclusory statement about the invention not being enabled for its full scope (middle of page 4 of Office Action dated April 11, 2006). However, no specific reasoning was set forth as to how these cited cases pertained the instant invention and what reasonable basis the Examiner had for believing that the claimed invention was unpredictable. This is one of the reasons why, in Applicants' response to the Office Action dated April 11, 2006, the Applicants' position was that the Examiner had not fulfilled her burden of establishing a reasonable basis for questioning the enablement for the claimed invention and had asked the Examiner for either an Examiner's affidavit or references to establish the unpredictability of the area of the claimed invention.

In the Advisory Action, the Examiner responds that she is not required to provide references to establish unpredictability. However, Applicants maintains that the Examiner is bound by MPEP § 2164.04, which sets forth the Examiner's initial burden to establish lack of enablement and mandates that "specific technical reasons are always required." In the Advisory Action, the Examiner's specific statement regarding unpredictability is that "[r]eferences are not required to establish unpredictability." While MPEP § 2164.04 does state this, there is a separate requirement that in the absence of references, the Examiner must provide specific technical reasons as to why this technology is unpredictable. The Examiner has not provided any technical reasons but rather, criticized the Applicants' data as a substitute. As such, Applicants maintain that the Examiner has not met her initial burden of establishing a reasonable basis for questioning the enablement because she neither provided specific technical reasons nor provided references to establish the unpredictability in this area of ISS technology.

Assuming *arguendo* that the Examiner did met her initial burden of establishing a reasonable basis for questioning the enablement, then Applicants believe that the instant invention is enabled for its full scope when one considers the Wands factors and the specification's disclosure in the context of what was known in the art at the time the patent application was filed.

MPEP §2164.01(a) states that “[t]here are many factors to be considered when determining whether there is sufficient evidence to support a determination that a disclosure does not satisfy the enablement requirement and whether any necessary experimentation is “undue.” These factors include, but are not limited to: (a) the breadth of the claims; (b) the nature of the invention; (c) the state of the prior art; (d) the level of one of ordinary skill; (e) the level of predictability in the art; (f) the amount of direction provided by the inventor; (g) the existence of working examples; and (h) the quantity of experimentation needed to make or use the invention based on the content of the disclosure.

#### Breadth of claims

The claims generally are directed to compositions of immunostimulatory sequences (ISS) with a pharmaceutically excipient wherein the ISS is less than about 200 nucleotides in length and comprise a particular structural formula set forth by SEQ ID NO: 62. Each position is further limited by what nucleotides can be at that specific position. In addition, the ISS cannot be of two particular sequences set forth as SEQ ID NO: 63 and SEQ ID NO: 64. The specification defines “ISS” as “polynucleotide sequences that effect and/or contribute to a measurable immune response as measured *in vitro*, *in vivo* and/or *ex vivo*.” The definition continues by setting forth methods by which one of skill in the art can measure this immune response. Importantly, the rest of the specification continues to define the ISS being claimed. The Examiner has fixated on the definition of “ISS” on page 11 of the specification to the exclusion of the rest of the specification. As the Examiner has correctly pointed out in her Office Action, the claims are construed in light of the specification. As such, these claims can be defined even further beyond the introductory definition presented on page 11 of the specification. For example, pages 23-32 details the different substitutions that can be made to generate a limited population of ISS. Thus, the claims are not as broad as the Examiner believes.

Level of predictability in the art

Another Wands factor, the unpredictability factor, is closely tied into the analysis for the breadth of the claims. MPEP § 2164.03 states that “[t]he amount of guidance or direction needed to enable the invention is inversely related to the amount of knowledge in the state of the art as well as the predictability in the art.” *In re Fisher*, 427 F.2d 833, 839 (CCPA 1970).

The area of ISS technology is not a nascent area of technology. Applicants have provided a number of references that describe various aspects of ISS technology starting at the bottom of page 3 and extending to the bottom of page 5 as well scattered throughout the specification. The crux of Examiner’s argument is that immunostimulatory responses cannot be predicted and as such, the claims are not enabled for the full scope. However, the fallacy of the Examiner’s argument is that it assumes that Applicants have claimed *all* ISS’s in general. This is clearly not the case as evidenced by all the restrictions recited in the claims for what an ISS can be or cannot be.

In the Advisory Action, after the sentence where the Examiner states that she does not need to cite references to establish unpredictability, the Examiner goes on to allege that Applicants teach that CpG-containing sequences induce Th2 responses. Specifically, the Examiner states that “[t]he fact that the full scope of the claims is not enabled is clearly recognized in the background [sic] of the disclosure that indicates that CpG sequences induce Th2 as opposed to Th1 cytokines (IL-4 or IL-5).” The Examiner also states that “[n]one of the other recited activities of immune stimulation IL-4, IL-5 have been demonstrated to be associated with recited sequences.”

Applicants strongly disagree with the Examiner’s characterization of Applicants’ teachings in the specification. Throughout the specification, Applicants have explained that ISS suppress Th2 responses and/or promote Th1-type responses, such as stimulation of interferon-alpha and interferon-beta. See, for example, page 3 lines 7-10, which teaches that ISS “induces an immune response with a Th1-type bias as indicated by secretion of Th1-associated cytokines. Administration of an immunostimulatory polynucleotide with an antigen results in a Th1-type

immune response to the administered antigen.” Also see, for example, page 66, lines 1-6 which explains that one of skill in the art can modulate immune response in mammal, preferably a human, by administering an ISS-containing polynucleotide such that “[i]mmunomodulation may include stimulating a Th-1 type immune response and/or inhibiting or reducing a Th2-type immune response.”

The Applicants note that, if the Examiner is referring to the Raz et al. *PNAS* paper on page 3 of the background section, this paragraph states that results from administration of an immunostimulatory polynucleotide are a Th-1 type immune response to the antigen. Reference to the secretion of IL-4 and IL-5 (Th2-type cytokines) was in response to intradermal administration of *E. coli* beta-galactosidase in saline or the adjuvant alum. But when ISS is administered, then the Th-2 type response seen before is now suppressed and the response shifts to a Th1-type response (page 3, lines 11-20). Applicants request clarification from the Examiner as to where the Applicants have reported production of IL-4 and IL-5 in response to ISS administration in the background section of the specification.

Applicants have limited their claims of ISS to specific structural forms (instead of claims to all types of ISS) and have disclosed throughout the specification that these particular ISS have produced Th1-type responses. As such, the amount of unpredictability in the type of specific ISSs being claimed is not high in view of the restrictions on the ISS structure as well as the Th1-type responses that Applicant have disclosed in the specification.

#### Nature of the invention

The nature of this invention is directed to immunomodulatory polynucleotides. However, Applicants have narrowed the claims to be directed only towards immunostimulatory polynucleotides. Applicants have addressed some of the technical features of ISS above. In addition, Applicants have referred to a number of publications in the specification that describe the nature of the invention. The analysis of this factor is closely tied to the state of the art at the time the application was filed.

State of the prior art

MPEP § 2164.03 states that “[t]he more that is known in the prior art about the nature of the invention, how to make, and how to use the invention, and the more predictable the art is, the less information needs to be explicitly stated in the specification. In contrast, if little is known in the prior art about the nature of the invention and the art is unpredictable, the specification would need more detail as to how to make and use the invention in order to be enabling. See, e.g., *Chiron Corp. v. Genentech Inc.*, 363 F.3d 1247, 1254 (Fed. Cir. 2004).

As evidenced by the number of references cited throughout the specification, particularly in the section starting from the bottom of page 3 to the bottom of page 5, the concept of using immunomodulatory sequences is hardly novel. Many other groups have published teachings on the workings of ISS since its discovery in the 1980's. Thus, the field of immunomodulatory sequences is not a nascent field of technology that would require extensive elaboration in the specification.

Amount of direction provided by the inventor

Applicants have disclosed, *inter alia*, the structure of particular types of ISS, how to measure some immune responses from the administration of the ISS, modifications that can be made to the ISS, antigens that can be used with the ISS and how to use these types of ISS for therapy. This disclosure, combined with the state of the art at the time the application was filed, provide more than adequate disclosure for one of skill in the art to practice the claimed invention.

Existence of working examples

MPEP § 2164.03 states that “[t]he scope of the required enablement varies inversely with the degree of predictability involved, but even in unpredictable arts, a disclosure of every operable species is not required.” On page 4 of the Office Action, dated April 11, 2006, the Examiner has cited case law to support her contention that in areas of art “where the results are unpredictable, the disclosure of a single species usually does not provide an adequate basis to support generic claims.”

However, the Examiner's reliance on case law where the finding of lack of enablement due to the existence of only one working example is misplaced. For example, the Examiner cites *In re Wright* 999 F.2d 1557 (Fed. Cir. 1993) on page 4 of the Office action. In *Wright*, the patentee had shown success with Prague Avian Sarcoma virus but tried to claim a generic claim to vaccines for pathogenic RNA viruses. *Id.* at 1558-1559. The patentee tried to rely on publications after the filing date to establish that one of skill in the art had success with other types of RNA viruses (e.g., HIV and SIV) other than his *single* working example. *Id.* at 1563-1564. The court rejected this argument as having no significance to what one of skill in the art would have believed at the time of filing of the application with respect to how the single working example could be extrapolated out to other types of RNA viruses and rejected the patentee's claim for generic coverage on vaccines for pathogenic RNA viruses.

In contrast to facts presented in the case law cited by the Examiner, the Applicants have provided a number of working examples to support their claims. As such, the number of working examples provided herein is sufficient basis for supporting the breadth of the claims being pursued.

Quantity of experimentation needed to make or use the invention based on the content of the disclosure

As discussed above, the amount of experimentation that one of skill in the art would need to perform to practice the invention is minimal. The specification teaches very specific sequence limitations for the ISS structures being claims. The specification also teaches the kind of assays that one of skill in the art could perform to determine the immune responses being generated by the ISS. In addition, the specification provides detailed teaching for how to make modifications to the ISS structures being claims as well how to use these ISS with antigens for treating various medical conditions. As such, the amount of experimentation needed to make or use the invention is low when one of skill in the art uses the detailed teachings of the specification combined the state of the art at the time the invention was filed.

Level of one of ordinary skill

This Wands factor is not in dispute here. As such, Applicants will not address this factor at this time.

In view of the foregoing, Applicants believe that the claims are fully enabled and respectfully request that the Examiner withdraw this rejection.

***Claim Rejections under 35 U.S.C. 102(e)***

In the Advisory Action, the Examiner has maintained the rejection of claims 1-3, 15-19, 26, and 48 under 35 U.S.C. 102(e) as allegedly being anticipated by Doucette-Stamm et al. (U.S. Patent No. 6,800,744 ('744 patent), issued October 5, 2004 with priority to provisional document 60/051,533 filed July 2, 1997) for reasons made of record in the Office Action mailed August 1, 2005. In the August 1, 2005 Office Action, the Examiner cited SEQ ID NO: 1794 and stated that nucleotide residues 37-46 of SEQ ID NO: 1794 was 100% identical to SEQ ID NO: 77 of the instant application. In the Advisory action, the Examiner stated that nucleic acid at hand is 480 base pairs (referring to SEQ ID NO: 1794 of the '744 patent) and that the art contemplates fragments that anticipate.

Applicants traverse this rejection and respectfully disagree with the Examiner's statements. For a reference to be anticipatory art, it must disclose in that single reference each and every limitation in the claim, either expressly or inherently. MPEP § 2131.02 states that "[a] genus does not always anticipate a claim to a species within the genus." In support of this notion, the Federal Circuit has stated that "[i]t is well established that the disclosure of a genus in the prior art is not necessarily a disclosure of every species that is a member of that genus... There may be many species encompassed within a genus that are not disclosed by a mere disclosure of the genus." *Atofina v. Great Lakes Chemical Corp.*, 441 F.3d 991, 999 (Fed. Cir. 2006).

The '744 patent fails to disclose each and every limitation in the claims. Claim 1 of the instant application has a maximum length of 200 nucleotides. In contrast, SEQ ID NO: 1794 of the

‘744 patent is 480 nucleotides long, as the Examiner correctly points out in the Advisory Action. As such, SEQ ID NO: 1794 does not anticipate the invention *per se* because its length of 480 nucleotides is longer than the 200 nucleotide maximum length recited by the claims.

It appears that the Examiner’s position is that a fragment within SEQ ID NO: 1794 anticipates the invention. However, the Examiner’s position runs contrary to the rules stated in MPEP § 2131.02 and further clarified by the Federal Circuit in *Atofina*. A careful review of the ‘744 patent reveals that it does not mention SEQ ID NO: 1794 at all, except for the sequence listing itself. The specification does not teach a composition of any fragments within SEQ ID NO: 1794. Importantly, the specification fails to teach a composition comprising nucleotides 37-46 of SEQ ID NO: 1794. Furthermore, there is no explicit teaching in the ‘744 patent of which fragments within SEQ ID NO: 1794 could be used for the composition being cited by the Examiner in the Advisory Action and past Office Actions. Applicants invite the Examiner to reference the column and line numbers in the ‘744 patent where there is explicit or implicit disclosure of the composition comprising nucleotides 37-46 of SEQ ID NO: 1794. Accordingly, the Examiner cannot ignore the Federal Circuit’s ruling in *Atofina* and conclude that every species of a nucleotide fragment that may reside within SEQ ID NO: 1794 is disclosed by the genus disclosure of SEQ ID NO: 1794, itself a 480 nucleotide fragment.

In addition, claim 1 also requires an additional element of a “pharmaceutically acceptable excipient” with the ISS. There is no teaching of a composition comprising nucleotides 37-46 of SEQ ID NO: 1794 in the ‘744 specification that also comprises a pharmaceutically acceptable excipient. Columns 6-7 of the ‘744 patent teaches the fragments of the sequences disclosed in the sequence listings are used as hybridization probes for diagnostic purposes. Hybridization probes are not used with pharmaceutically acceptable excipient. Accordingly, the ‘744 patent does not anticipate the claimed invention of the instant application since it does not recite each and every element of the claimed invention.

In view of the foregoing, Applicants respectfully request that the Examiner withdraw this rejection.

## CONCLUSION

In view of the above, each of the presently pending claims in this application is believed to be in immediate condition for allowance. Accordingly, the Examiner is respectfully requested to withdraw the outstanding rejection of the claims and to pass this application to issue. If it is determined that a telephone conference would expedite the prosecution of this application, the Examiner is invited to telephone the undersigned at the number given below.

In the event the U.S. Patent and Trademark office determines that an extension and/or other relief is required, applicant petitions for any required relief including extensions of time and authorizes the Commissioner to charge the cost of such petitions and/or other fees due in connection with the filing of this document to **Deposit Account No. 03-1952** referencing docket no. **377882001800**. However, the Commissioner is not authorized to charge the cost of the issue fee to the Deposit Account.

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